UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/766,435	01/27/2004	Heinz Schaller	SCHALLER 2/1	4011

28157 7590 09/07/2005

URSULA B. DAY, ESQ.
350 FIFTH AVE.
SUITE 3220
NEW YORK, NY 10118

EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 09/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/766,435	SCHALLER ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 21-34 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 21-34 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 1/27/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

New claims 21-34 are pending in the present application, and they are examined on the merits herein.

Claim Objections

Claims 22 and 29 are objected to because the phrase "the replication defective hepadnavirus particles are **one** of human hepatitis B virus or duck hepatitis B virus" is not grammatically correct. Appropriate correction is required.

New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-26 and 29-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 21 and its dependent claims recite the limitation "deleting from the S-gene of a hepadnavirus at least 200 nucleotides sequences". Claim 29 and its dependent claims recite the limitation "deleting at least 200 base pair sequences". There is **no written support** for these recited limitations that encompass the deletion of 200

sequences containing base pairs or nucleotides. The originally filed specification teaches that the length of replaced nucleotide sequence (e.g., the hepadnaviral S gene) is at least about 200, preferably at least about 300 or 400, and even more preferably about 500 or 600 base pairs in length (at least page 12, lines 8-12; page 15, lines 33-36). **Thus, it is apparent that Applicants did not contemplate to delete 200 sequences containing base pairs or nucleotides in the S gene of a hepadnavirus or a hepatitis B virus at the time the application was filed.** Applicants also fail to point out the exact page number and line number in the instant specification that provide a written support for these new limitations.

Therefore, given the lack of guidance provided by the originally filed specification, it would appear that Applicants did not contemplate or have possession of the claimed invention at the time the application was filed.

Claim Rejections - 35 USC § 112

Claims 21-23, 26, 29-31 and 34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

An *in vitro* method for expressing a heterologous gene in hepatocytes comprising:

- providing replication defective hepadnavirus particles at a titer level competent to infect hepatocytes by deleting and replacing at least 200 nucleotides of the S-gene of a hepadnavirus with a non-hepadnaviral DNA of up to 800 base pairs encoding a cytokine or a chemokine such

that the sequences that are essential for reverse transcriptase are retained and the heterologous gene is expressed under the control of the endogenous S promoter;

- infecting hepatocytes with the hepadnavirus particles such that the heterologous gene is delivered into the hepatocytes and expressed in the hepatocytes;

and an *in vitro* method for producing the same replication defective recombinant hepanavirus particles;

does not reasonably provide enablement for an *in vitro* method for expressing a heterologous gene in hepatocytes or an *in vitro* method for producing replication defective recombinant hepadnavirus particles capable of expressing a heterologous gene in hepatocytes, wherein a non-hepadnaviral DNA of up to 800 base pairs encoding a cytokine or a chemokine can be inserted at **any other sites** in a hepadnaviral or hepatitis B virus genome. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification is not enabled for the instant broadly claimed invention for the reasons discussed below.

(a) The breadth of the claims

The instant claims encompass an *in vitro* method for expressing a heterologous gene in hepatocytes or an *in vitro* method for producing replication defective recombinant hepadnavirus particles capable of expressing a heterologous gene in

hepatocytes, wherein a non-hepadnaviral DNA of up to 800 base pairs encoding a cytokine or a chemokine can be inserted at **any site** in a hepadnaviral or hepatitis B virus genome, not necessarily limited that the non-hepadnaviral DNA is inserted at the site where the S gene has been deleted or replaced.

(b) The state of the prior art and the unpredictability of the art

A hepadnaviral or hepatitis B virus (HBV) based vector is well known for its size constraint, particularly with respect to the infectivity of the recombinant hepadnaviruses. It is also known that the tiny hepadnaviral genome (3 kb) is virtually blanketed with critical cis-acting elements—initiation sites for minus and plus strand DNA synthesis, promoter elements for multiple critical transcripts, and numerous sequences affecting RNA transport, processing, stability, and packaging (Ganem, Proc. Natl. Acad. Sci. 96:11696-11697, 1999; page 11696, col. 3, middle of the last paragraph). Ganem further teaches that the viral reverse transcriptase acts preferentially in *cis* and is only inefficiently supplied in *trans*, for reasons that are still incompletely understood and that most substitutions in the genome of a hepadnaviral or hepatitis B virus genome will interrupt the reverse transcriptase coding region (page 11697, col. 1, first paragraph). Even a year after the effective filing date of the present application (8/26/1998), Protzer et al. (Proc. Natl. Acad. Sci. 96:10818-10823; 1999; IDS) still state "Despite these precautions (with respect to care taken not to exceed the authentic genome size and not to affect *cis*-acting control elements), among the several constructs in which different genome segments were replaced, **only substitution of the small envelope (S) gene by foreign sequences turned out to be successful**" (page 40820, col. 2,

bottom of first paragraph). Thus, it is apparently that only after a diligent screening of many recombinants, the coding region for the major viral envelope glycoprotein S in a hepadnaviral genome is the only region that lacks important *cis*-acting sequences and therefore tolerates substitution with foreign DNA that results in the production of recombinant hepadnavirus particles capable of infecting and expressing a heterologous gene in hepatocytes.

(c) The amount of direction or guidance presented

Apart from the exemplification showing the preparation of rDHBV-IFN, rDHBV-GFP and rHBV-GFP particles in which a heterologous gene encoding a green fluorescent protein or a duck type I interferon (less than 800 nucleotides) substituted or replaced the hepadnaviral S gene at its location, the instant specification fails to provide sufficient guidance for a skilled artisan on how to insert the non-hepadnaviral DNA encoding a cytokine or a chemokine at any other sites or locations in a hepadnaviral genome to generate the desired recombinant hepadnaviral particles for infection and expression of the heterologous gene in hepatocytes *in vitro*. In light of the teachings of Ganem and Protzer et al. discussed above, coupled with the lack of sufficient guidance provided by the present disclosure, it would have required undue experimentation for a skilled artisan on a trial and error basis to make and **use** the instant broadly claimed invention.

Additionally, the courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in the patent application (27 USPQ2d 1662 *Ex parte Maizel.*).

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the aforementioned issues, the state of the relevant art and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 28 recites the method of claim 27. However, claim 27 is drawn to a replication defective hepadnavirus particle. Therefore, the metes and bounds of the claim are not clearly determined because it is unclear which method steps are involved in the method of claim 28. Clarification is requested. However, for the purpose of a compact prosecution, Examiner assumes that Applicants intend to claim a replication defective hed\padnavirus particle in claim 28 rather than a method. Additionally, it is unclear what is encompassed by the phrase "one of an authentic AUG codon of the S-gene of nucleotides encoding further amino acids of the S-protein are fused in frame".

In claim 29 and its dependent claims, there is no nexus among the steps of deleting, inserting and producing a recombinant hepadnavirus. For example, inserting a heterologous gene of up to 800 base pairs into what and wherein? Which sequences do Applicants refer to in the phrase "the sequences that are essential for reverse

transcriptase are retained"? Additionally, the step of producing a recombinant hepadnavirus only requires a means of a helper plasmid. Furthermore, the term "the hepatocyte" on lines 14-15 also renders the claims indefinite because which hepatocytes do Applicants refer to? It is noted that prior to this recitation, claim 29 recites hepatocytes. Clarification is requested because the metes and bounds of the claims are not clearly determined.

In claim 33, the phrase "one of an authentic AUG codon of the S-gene of nucleotides encoding further amino acids of the S-protein are fused in frame" renders the claim indefinite. This is because it is unclear what exactly Applicants intend to claim. Once again, clarification is requested because the metes and bounds of the claim are not clearly determined. For the purpose of a compact prosecution, Examiner assumes that Applicants intend to incorporate the phrase "one of an authentic AUG codon of the S gene or its nucleotides encoding further amino acids of the S-protein" into the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 21-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horwich et al. (WO 90/02176; IDS) in view of Alber et al. (U.S. Patent No. 5,928,636).

Horwich et al. disclose the preparation of replication defective hepadnaviruses and in particular two types of defective hepadnavirus genomes, and the nucleic acid sequences thereof (see abstract and pages 15-18). Horwich et al. disclose the first type ("particle defective" genomes) are incapable of supplying all hepadnaviral functions required for replication, but are able to produce a pregenome RNA with the appropriate *cis*-acting signals necessary for inclusion of the RNA in virions ("packaging") and for reverse transcription into DNA. The second type of defective hepadnavirus genomes ("packaging genomes") produced pre-genomic RNA which can not be packaged and/or reverse-transcribed into a double-stranded genomic DNA, and produce messenger RNAs capable of supplying functions required *in trans* for packaging. Horwich et al. further teach that hepadnavirus virion particles containing a particle-defective genome can be produced by coexpression of the particle-defective genome and "helper" hepadnavirus packaging genome(s). The resulting hepadnavirus containing a particle-defective genome can then be used for the infection of a hepatocyte, to which the

particle-defective DNA is delivered and in which it can be expressed (page 16, second paragraph). Horwich et al. specifically teach to make permanent hepatic cell lines stably transfected with defective hepadnaviral genomes (packaging cell lines) that are capable of supplying necessary functions to defective hepadnaviral genomes and producing defective infectious particles (see page 18, first full paragraph). Horwich et al. teach the generation of several defective hepadnavirus genomes including those of hepatitis B virus pathogenic in humans, duck hepatitis B virus and others (see section 5.1.1 on page 29). Horwich et al. teach that their defective hepadnavirus virion particles containing a heterologous gene sequence which encodes for an immunogenic epitope (an agent that modulates a host immune response) or **hepatic enzymes or a product which is toxic to a given pathogen that is the causative agent of a disorder affecting the liver** (see section 5.1.3.1 on page 38, and section 5.2 on page 44, particularly first full paragraph on page 45). Horwich et al. specifically teach that **the heterologous gene sequence replaces the gene coding for the surface antigen, and specifically that the recombinant hepadnavirus DNA can retain pre-S DNA sequences which contain promoters for surface antigen expression** (page 49, lines 1-5, and section 6.7 on page 69 for **the exemplification** showing the preparation of the S1 particle-defective genome by replacing the KpnI-XbaI fragment, 68 bp, located between nucleotide positions 1290 and 1358, of the DHBV wild-type sequence with a synthetic linker **of the same size**). Horwich et al. further teach that specific initiation signals are also required for efficient translation of inserted protein coding sequences. These signals include the ATG initiation codon and adjacent sequences. The initiation

codon must be in phrase with the reading frame of the protein coding sequences to ensure the translation of the entire insert (see page 35, first full paragraph).

Horwich et al. do not specifically teach the utilized heterologous gene encodes for a cytokine, a chemochine or any one of IFNalpha, IFNbeta, IFNgamma, TNFalpha, IL-18 or IL-12.

However, at the effective filing date of the present application, Alber et al. teach that IFNalpha has proven to be effective in the treatment of viral infections, e.g., both HBV and HCV infections (col. 2, lines 1-3). Alber et al. also teach that the combined use of IFNalpha and IL-12 is useful for treating chronic infectious viral diseases including hepatitis B, hepatitis C, HIV and others due to the synergistic interaction of IFNalpha and IL-12 (see abstract). Alber et al. also note that interferon cDNAs and IL-12 cDNA are available in the prior art, and therefore interferons and IL-12 can be produced recombinantly by methods known in the art for the preparation of their pharmaceutical formulations (see col. 1, lines 59-67; col. 4, lines 18-25).

Accordingly, it would have been obvious and within the scope of skill for an ordinary skilled artisan to modify the replication defective recombinant hepadnaviruses, and methods for expressing a heterologous gene in a hepatocyte, and for producing replication defective recombinant hepadnavirus particles taught by Horwich et al. by using a gene encoding IFNalpha or other interferons (e.g., IFNgamma) or IL-12 as the heterologous gene as a replacement for a region in the S gene of the hepadnaviral genome in light of the teachings of Alber et al. This replacement would result in the deletion of at least 200 nucleotides in the S gene of a hepadnavirus genome and the

heterologous gene encoding a cytokine or a chemokine would be less than 800 nucleotides. Please also note that Horwich replaced a deleted fragment of the S-gene with a heterologous sequence of the same size in an exemplification.

An ordinary skilled artisan would have been motivated to carry out the above modification to produce recombinant interferons or IL-12 in a hepatocyte expression system because interferons and IL-12 are useful for treating chronic liver infectious diseases such as hepatitis B and hepatitis C. Alternatively, one of ordinary skilled artisan would have been motivated to carry out the above modification to investigate the effectiveness of the modified replication defective recombinant hepadnavirus particles expressing IFNalpha or IFNgamma or IL-12 in an animal model of chronic liver infectious diseases.

Accordingly, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Dave Nguyen, at (571) 272-0731.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

QUANG NGUYEN, PH.D
PATENT EXAMINER